Echocardiography plays an evolving and important role in the care of heart failure patients treated with biventricular pacing, or cardiac resynchronization therapy (CRT). Numerous recent published reports have utilized echocardiographic techniques to potentially aid in patient selection for CRT prior to implantation and to optimized device settings afterwards. However, no ideal approach has yet been found. This consensus report evaluates the contemporary applications of echocardiography for CRT including relative strengths and technical limitations of several techniques and proposes guidelines regarding current and possible future clinical applications. Principal methods advised to qualify abnormalities in regional ventricular activation, known as dyssynchrony, include longitudinal velocities by color-coded tissue Doppler and the difference in left ventricular to right ventricular ejection using routine pulsed Doppler, or interventricular mechanical delay. Supplemental measures of radial dynamics which may be of additive value include septal-to-posterior wall delay using M-mode in patients with non-ischemic disease with technically high quality data, or using speckle tracking radial strain. A simplified post-CRT screening for atrioventricular optimization using Doppler mitral inflow velocities is also proposed. Since this is a rapidly changing field with new information being added frequently, future modification and refinements in approach are anticipated to continue.

Keywords: Echocardiography, Doppler ultrasound, Congestive Heart Failure, Pacing Therapy
LV ejection fraction (EF) less than or equal to 35%. Despite the great or IV, widened QRS greater than or equal to 120 milliseconds, and heart failure: New York Heart Association (NYHA) functional class III approved recommendations for CRT include patients with severe mitral regurgitation (MR) and improvements in LV function. Currently approved recommendations for CRT include patients with severe heart failure: New York Heart Association (NYHA) functional class III or IV, widened QRS greater than or equal to 120 milliseconds, and LV ejection fraction (EF) less than or equal to 35%. Although the great success of randomized clinical trials, approximately 25% to 35% of patients undergoing CRT do not respond favorably. Echocardiographic and Doppler imaging techniques have emerged to play a potential role in the care of the patient with CRT. Although there are several potential reasons for nonresponse to CRT, it has been suggested that the ECG widened QRS is a suboptimal marker for dyssynchrony, and that echocardiographic quantification of dyssynchrony may potentially play a role in improving patient selection for CRT. The PROSPECT study (predictors of responders to CRT) was a recent observational multicenter study from Europe, the United States, and Hong Kong. Although final data from this study are not yet available, the preliminary findings highlighted the complexity of technical factors that influence dyssynchrony analyses and the importance of training and expertise of individual laboratories to achieve reliable results. The PROSPECT study suggested that there are technical issues related to variability that are not yet resolved, and that future work is needed to improve reproducibility of dyssynchrony analysis.

### OVERVIEW OF MECHANICAL DYSSYNCHRONY

Electrical activation in the normal heart typically occurs quickly within 40 milliseconds via conduction through the Purkinje network and is associated with synchronous regional mechanical contraction. A variety of myocardial diseases induce alterations in cardiac structure and function that result in regions of early and late contraction, known as dyssynchrony. Although other authors have used the term “asynchrony” interchangeably, we will use the term “dyssyn-
chrony” in this report to describe this phenomenon. Mechanical dyssynchrony is usually associated with a prolonged QRS duration on the surface ECG, although it may also exist in a subset of patients with heart failure and depressed LV function and narrow QRS by ECG.20,21 This report will focus on patients with wide QRS duration, because this is the current clinical practice for CRT.

Three types of cardiac dyssynchrony may occur: intraventricular, interventricular, and atrioventricular (AV). Abnormalities of timing of regional mechanical LV activation, known as intraventricular dyssynchrony, appear to be the principal factor associated with contractile impairment and affected by CRT. Accordingly, many echocardiographic Doppler parameters focus on intraventricular dyssynchrony, and we will use the term “dyssynchrony” throughout this report when referring to “intraventricular dyssynchrony,” unless otherwise stated. The classic type of dyssynchrony resulting from abnormal electrical activation is seen with left bundle branch block. The typical pattern seen with left bundle branch block is early activation of the interventricular septum and late activation of the posterior and lateral LV walls.19 The early septal contraction occurs before normal ejection when LV pressure is low and does not contribute to ejection. This process generates heterogeneous stress and strain in the LV, with one wall exerting forces on the contralateral wall. Typically early septal contraction causes posterior-lateral stretching or thinning, followed by late posterior-lateral contraction causing septal stretching or thinning.22 Dyssynchrony results in inefficient LV systolic performance, increases in end-systolic volume and wall stress, and delayed relaxation that is thought to affect biological signaling processes involved in regulating perfusion and gene expression.23 Improvements in LV synchrony are associated with LV functional improvements and reduction in MR.8,24-28

GENERAL APPROACH TO QUANTIFYING MECHANICAL DYSSYNCHRONY

Because the vast majority of patients with wide QRS appear to have mechanical dyssynchrony, an important goal of imaging is to improve patient selection for CRT by identifying the subset of patients with wide QRS but no mechanical dyssynchrony. The pathophysiologic reason for this scenario is unclear, but it appears that patients with minimal to no dysynchrony have a lower probability of response to CRT and appear to have a poor prognosis after CRT.15 There are other reasons for not responding to CRT, including ischemic disease with too much scar to reverse remodel, subsequent infarction after CRT, suboptimal lead placement, and other factors not yet defined.24,29-33 Accordingly, the absence of dysynchrony is only one factor for nonresponse, but one that potentially can be identified prospectively by echocardiographic Doppler methods.

Results from the PROSPECT study illustrated that technical factors of individual echocardiographic Doppler methods, such as feasibility and reproducibility, affect results in a multicenter setting.17,18 Quantifying mechanical dyssynchrony in a series of patients with heart failure is complex, and no single ideal method currently exists. However, a practical approach that considers several factors is currently recommended to assist in determining that a patient has or does not have significant dysynchrony. Ambiguities that may occur in analysis using different approaches must be adjudicated on a case-by-case basis. A reasonable starting point is to examine the routine 2-dimensional (2D) echocardiographic images. Trained observers can often assess dyssynchrony visually as an early septal in-and-out motion described as septal flash or bounce in typical left bundle branch block dyssynchrony. Because the presence or absence of dyssynchrony may be subtle in many patients with severe heart failure, visual assessment should not stand alone and the use of quantitative echocardiographic Doppler tools is advocated.

M-MODE

The technically simplest approach to quantify LV dyssynchrony is with conventional M-mode echocardiography that records septal-to-posterior wall-motion delay (Figure 1, A).

1. Step 1: Select either the parasternal long-axis or short-axis views.
2. Step 2: Position the M-mode cursor at the midventricular level (papillary muscle level).
3. Step 3: Set sweep speed to 50 to 100 mm/s.
4. Step 4: Identify the time delay from peak inward septal motion to peak inward posterior wall.

Pitzalis et al reported a cut-off value of greater than or equal to 130 milliseconds as a marker of LV dyssynchrony in a pilot series of 20 patients principally with nonischemic cardiomyopathy with a sensitivity of 100% and specificity of 63% to predict a greater than or equal to 15% decrease in LV end-systolic volume index, and improvements in clinical outcome.34,35 Longer delays in septal to posterior wall-motion delay were associated with greater reverse remodeling. Measurement of the septal-to-posterior wall-motion delay by M-mode may be difficult in many patients because of complex septal motion that is both active and passive–wall-motion abnormalities involving the septum or posterior wall. Marcus et al highlighted these limitations in an analysis of M-mode data from 79 patients in the CONTAK-CD trial.36 They found the reproducibility of M-mode measurements to be unsatisfactory, with responders (defined as ≥15% reduction in LV end-systolic volume) having septal-to-posterior wall-motion delays similar to nonresponders. The PROSPECT study also identified a high degree of variability in analysis.17,18 Therefore, M-mode is not advocated to be used in isolation to quantify dyssynchrony, but may be considered as supplemental to other approaches, such as tissue Doppler (TD). In particular, the utility of M-mode in patients with ischemic cardiomyopathy has not been well demonstrated.

COLOR TD M-MODE

The addition of color TD M-mode is a useful adjunct to M-mode determination of LV dyssynchrony (Figure 1, B). Changes in direction are color coded, which may aid in identifying the transition from inward to outward motion in the septum and posterior wall. The same septal-to-posterior wall-motion delay greater than or equal to 130 milliseconds is considered to be significant dysynchrony, although this method is affected by similar limitations with routine M-mode as described above.

LONGITUDINAL TD VELOCITY

The largest body of literature to quantify dyssynchrony is represented by the assessment of longitudinal LV shortening velocities using TD from the apical windows.14-16,37-49 This is the principal method currently in clinical use, although it has limitations discussed subsequently. There are two basic approaches: color-coded or pulsed TD.

COLOR TD DATA ACQUISITION

Color TD data acquisition is simpler and more practical than pulsed TD and is the preferred method by consensus of this committee if
high frame rate color TD echocardiographic equipment is available. High frame-rate color TD, usually greater than 90 frames/s, is available in several major equipment vendors with recent hardware and software. Individual variations in color TD between ultrasound systems may exist, but these details have not yet been elucidated.

Step 1: Adjust the ECG to be noise free with a delineated QRS waveform.

Step 2: Optimize 2D imaging to insure maximal apical-to-near field left atrial imaging, with overall gain and time gain control settings adjusted for clear myocardial definition.

Step 3: Position the LV cavity in the center of the sector and aligned as vertically as possible, to allow for the optimal Doppler angle of incidence with LV longitudinal motion.

Step 4: Set the depth to include the level of the mitral annulus.

Step 5: Activate color TD and adjust the sector to include the entire LV with a goal of achieving high frame rates (usually >90 frames/s). Decrease depth and sector width to focus on the LV to increase frame rates, as needed. Adjust overall color gain for clear delineation of the myocardium. If available, the online color coding of time to peak velocity data may be activated.

Figure 1 Routine M-mode (A) at midventricular level and color-coded tissue Doppler M-mode (B) demonstrating septal to posterior wall delay of 180 milliseconds, consistent with significant dyssynchrony (≥130 milliseconds).
Step 6: Suspend patient breathing. Because low velocity TD data are affected by respiratory motion, we recommend that patients be instructed to hold their breath transiently if they are able, while a 3- to 5-beat digital capture is performed. This is usually at end expiration, but may be the phase with the optimal image quality. The number of beats captured should be increased if atrial or ventricular premature complexes are present.

Step 7: Record 3 standard imaging planes: apical 4-chamber view, apical 2-chamber view, and apical long-axis view.

Step 8: Determine the LV ejection interval. This is usually done using pulsed Doppler from an apical 5-chamber or apical long-axis view where the LV outflow tract is seen and velocity recorded (Figure 2).

COLOR TD DATA ANALYSIS

A major advantage of color DTI is the ability to analyze time-velocity data offline. The details for analysis vary by ultrasound vendor, but the general steps are similar.

Step 1: Determine the timing of LV ejection, usually from the beginning to the end of pulsed Doppler flow of the LV outflow tract. The details vary according to ultrasound system used, but timing usually is performed using the ECG as a time marker. The timing of beginning ejection to end ejection is then superimposed as the ejection interval on the subsequent time-velocity curve analysis.

Step 2: Size and place regions of interest (a minimum of 5×10 mm to 7×15 mm) in the basal and mid region of opposing LV walls (4 regions/view) to determine time-velocity plots.

Step 3: If possible, identify components of velocity curve, as a check for physiologic signal quality. These include isovolumic contraction velocity (usually <60 milliseconds from the onset of the QRS), the systolic wave, or S wave, moving toward the transducer and the early diastolic, or E wave, and late diastolic, or A wave, moving away from the transducer (Figures 3 and 4).

Step 4: Manually adjust the regions of interest within the segment both longitudinally and side-to-side within the LV wall to identify the site where the peak velocity during ejection is most reproducible. This is an important step to search for the most reproducible peak of greatest height, in particular where there is more than one peak or signal noise. If fine tuning of the region of interest fails to produce a single reproducible peak during ejection, the earlier peak is chosen if there are two or more peaks of the same height.

Step 5: Determine time from onset of the QRS complex to the peak systolic velocity for each region: 4 segments per view, for each of 3 views, for a total of 12 segments. An alternative is to determine the difference in the time to peak S wave from opposing walls, as described in the opposing wall delay method below. This is simply the time from the S wave of one wall to the S wave of the opposing wall on the same cineloops, and does not require measuring the onset from the QRS.

Step 6: Average the time to peak values in captured beats to improve reproducibility, because beat-to-beat variability may occur. A minimum of averaging 3 to 5 beats is recommended, with the number of averaged beats increased if beat-to-beat variability is encountered, excluding sequences with atrial or ventricular premature complexes. Analysis of TD data in atrial fibrillation is especially complex and problematic, and no data are currently available to support dyssynchrony analysis in this scenario.

POSTSYSTOLIC SHORTENING VELOCITIES

Some previous studies have included postsystolic shortening (positive myocardial velocity after aortic valve closure, which may be greater than the ejection peak) in their dyssynchrony analysis. The greatest sensitivity and specificity for predicting response to CRT appears to be attained when limiting peak longitudinal velocities for dyssynchrony analysis to the interval from aortic valve opening to aortic valve closure. Notabartolo et al measured the maximal difference in the time to peak systolic velocity including postsystolic shortening from the 6 basal segments. An average cut-off value greater than 110 milliseconds has a high sensitivity at 97%, but decreased specificity at 55% to predict LV reverse remodeling. Although the optimal approach has not yet been completely clarified, the current weight of evidence favors analysis of peak velocities during the ejection interval.
Figure 3. Color-coded tissue Doppler study from 3 standard apical views of patient who responded to resynchronization therapy. Time-velocity curves from representative basal or midlevels are shown. Maximum opposing wall delay was seen in apical long-axis view of 140 milliseconds between septum and posterior wall, consistent with significant dyssynchrony (>65 milliseconds).
Figure 4 Color-coded tissue Doppler study from 3 standard apical views of patient who did not respond to resynchronization therapy. Time-velocity curves from both basal and midlevels show no significant opposing wall delay less than 65 milliseconds.
CLINICAL STUDIES USING COLOR TD

The majority of studies have used color-coded TD to assess LV dyssynchrony and predict outcome, and it is the consensus of this writing group that this is currently the preferred approach. The simplest TD approach to identify LV dyssynchrony by color-coded TD uses the basal segments of the apical 4-chamber view to measure the septal-to-lateral delay, known as the two-site method. Subsequently, a 4-segment model was applied that included 4 basal segments (septal, lateral, inferior, and anterior). An opposing wall delay greater than or equal to 65 milliseconds allowed prediction of both clinical response to CRT (defined by an improvement in NYHA class and 6-minute walking distance) and reverse remodeling (defined as a 15% reduction in LV end-systolic volume). In addition, patients with LV dyssynchrony greater than or equal to 65 milliseconds had a favorable prognosis after CRT. An extension of this opposing wall delay method has included data from the 3 standard apical views: 4-chamber, 2-chamber, and long-axis. The maximum difference in time-to-peak velocity values among the 4 sites from each of the 3 apical views is determined as the maximal opposing wall delay. An important feature of this 3-view model is that it includes the anterior-septum and posterior walls seen in the apical long-axis view, which often has dyssynchrony. Yu et al developed a 12-segment SD model using color TD that also integrates information from the same 3 apical views (4-chamber, 2-chamber, and long-axis). The mechanical dyssynchrony index, also known as the Yu index, was derived from calculating the SD of the time-to-peak systolic velocity in the ejection phase 12-site standard deviation. A 12-site standard deviation cut-off value of greater than or equal to 33 milliseconds was derived from the healthy population to signify mechanical dyssynchrony. Yu et al used TSI color coding to guide placement of regions of interest and assess an antero-septal-to-posterior wall delay greater than or equal to 65 milliseconds from time-velocity curves to predict acute improvement in stroke volume after CRT. Yuet al also used TSI in 56 patients and found the Ts-SD derived by TSI from 12 LV segments had a highest receiver operating characteristic curve area of 0.90. Inclusion of postsystolic shortening in the model significantly reduced the receiver operating characteristic curve area to 0.69. Furthermore, all of the TSI parameters showed a slight, but consistently lower, predictive value than data derived directly from the time-velocity curves. Thus, it is recommended that myocardial time-velocity curves be examined with adjustment of regions of interest as described above to ensure the accuracy of the true peak velocities when TSI is used.

PULSED TD

Pulsed TD has been described as a means to assess dyssynchrony and is available on most echocardiography systems. Briefly, pulsed TD presets must be optimized on the echocardiographic system as recommended by the individual manufacturers. The general approach is as described above in the step-by-step color TD data acquisition and analysis sections, with modifications. The pulsed sample volume is set to approximately 1-cm length, the velocity scale set to maximize the time-velocity curve, and the
sweep speed set to 50 to 100 mm/s. Unlike offline color TD data analysis, the step where the sample volume is moved within the segment to search for a reproducible time-velocity signal must be done online. This is a major disadvantage of pulsed TD because it is time-consuming and susceptible to influences of breathing, patient movement, and alterations in heart rate. In addition, the timing of the ejection interval must be transferred manually. Furthermore, the peak velocity may be difficult to identify because of a broad spectral display with a plateau during systole. Because of these technical limitations, color-coded TD is the approach preferred by this writing group. Currently, clinical studies of pulsed TD to predict response to CRT are less numerous than those using color TD. Penicka et al used pulsed wave TD to measure the time of onset of the systolic signal of basal segments from the apical 4-chamber and long-axis views and the lateral right ventricular (RV) wall. Using a composite index of interventricular and intraventricular dyssynchrony longer than 100 milliseconds, they achieved 88% accuracy in identifying all but 6 patients who responded to CRT.

Figure 6 Pulsed tissue Doppler demonstrating dyssynchrony with delayed time to onset systolic velocity in lateral wall, as compared with septum in patient with left bundle branch block before resynchronization therapy.

TD LONGITUDINAL STRAIN, STRAIN RATE, AND DISPLACEMENT

Strain and strain rate imaging have the theoretic advantage of differentiating active myocardial contraction or deformation from passive translational movement and have been utilized to identify dyssynchrony. Comparing myocardial velocities and strain rate, Breithardt et al found an association between regional myocardial motion (expressed by velocity parameters) and deformation (expressed by strain rate imaging parameters). They concluded that the degree of dyssynchrony was not completely represented by the timing of myocardial velocity, particularly in ischemic heart disease, and that the timing of deformation should be the preferred modality. Sogaard et al found that the extent of delayed
longitudinal contraction at the base predicted improvement in EF after CRT.\textsuperscript{41,42} However, Yu et al demonstrated that parameters of strain rate imaging are not useful to predict reverse remodeling response.\textsuperscript{43,44,53} Currently, TD strain rate is restricted by a poor signal-to-noise ratio, which adversely affects reproducibility. On the other hand, improvements in strain analysis, including software developments such as strain determined by speckle tracking of routine gray-scale images, are promising as useful markers of systolic dyssynchrony.\textsuperscript{54}

Displacement imaging uses TD data to calculate the distance of myocardial movement, and is typically color coded and overlaid onto 2D images. The signal-to-noise ratio is more favorable than strain or strain rate imaging, but displacement is also affected by passive motion, and the Doppler angle of incidence. Improvements in displacement or tissue tracking have been described after CRT, however, cut-off values for predicting response and clinical outcomes after CRT have not yet been established.\textsuperscript{42}

**RADIAL STRAIN**

Because radial thickening is a major vector of LV contraction, and short-axis dynamics are important markers of dyssynchrony,\textsuperscript{55} it is

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**Figure 7** Doppler tissue images demonstrating longitudinal strain in healthy synchronous patient (A) and in patient with left bundle branch block before (B) resynchronization therapy.

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reasonable to utilize this information in a comprehensive examination. Strain has an advantage over M-mode of differentiating active from passive motion and identifying radial mechanical activation. Dohi et al first used TD strain to quantify radial mechanical dyssynchrony in 38 patients who underwent CRT. Radial strain was calculated from TD velocity data from the anteroseptum and posterior wall in the mid LV short-axis view. Disadvantages of TD radial strain included signal noise without adequate image quality and the effect of the Doppler angle of incidence.

A more recent approach is application of a speckle-tracking program that is applied to routine gray-scale echocardiographic images, which is not limited by Doppler angle of incidence. Suffoletto et al studied 64 patients undergoing CRT. Speckle tracking applied to routine midventricular short-axis images determines radial strain from multiple points averaged to 6 standard segments (Figure 8). Baseline speckle-tracking radial dyssynchrony (defined as a time difference in peak septal to posterior wall strain ≥ 130 milliseconds) predicted a significant increase in LV EF, with 89% sensitivity and 83% specific-

Figure 8 Speckle-tracking images demonstrating synchrony of peak segmental radial strain in healthy individual (A) and severe dyssynchrony in patient with heart failure and left bundle branch block (LBBB) referred for resynchronization therapy (B).